

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Hartmut Löbermann, Karl-Heinz Caster
Application NO.: 10/772,033
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FOR: Hydrates of optionally substituted 2-(2-Pyridinyl) Methylthio-1H-benzimidazoles and method for the production thereof

DECLARATION UNDER 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Dr. Löbermann, Hartmut, hereby declare as follows:

1. I am a citizen of Germany, residing at Beckerstrasse 7a, D-52078 Aachen, Germany.
2. I studied chemistry and received a PhD degree in chemistry in the year 1982.
3. Since 1984, I have been employed as a research chemist in the field of blood coagulation and from 1990 up to now I have been working as head of the bulk pharmaceutical production for the company of Grünenthal GmbH at Aachen, Germany.
4. I am an inventor of the invention disclosed in the US Patent Application Serial No. 10/772,033.

5. The compound pyrimetazol - [5-Methoxy-2-(4-methoxy-3,5-dimethyl-pyridin-2-ylmethyl-sulfanyl)-1H-benzo-imidazole] - was prepared under my supervision and control according to the procedure described in US Patent Application Serial No. 10/772,033.

6. The following experiments were carried out under my supervision and control:

A.

Determination of loss on drying of pyrimetazol [5-Methoxy-2-(4-methoxy-3,5-dimethoxy-pyridin-2-ylmethyl-sulfanyl)-1H-benzimidazol]

The determination of loss on drying was carried out using the following equipment manufactured by the company Mettler Toledo: halogen dehumidifier HR 73 Serial Number 1118490269 and weighing scale aluminium HA-D90 Serial Number 13865.

The samples were measured under the following conditions:

sample quantity: 5,000 g ± 0,500 g, drying temperature: 60 °C (fast drying), shutdown criteria: 3, depiction of results: 0-100 % MC (moisture content) (printing window 1 min)

The determination of loss on drying was carried out by loading the method PHB 8.E.6 first, naming the sample, putting the sample quantity on weighing scale HA-D90 and finally starting analysis

Calculation:

The automatic calculation is done according to the following formula:

$$\frac{\text{initial weight (g)} - \text{dry mass (g)}}{\text{initial weight (g)}} \times 100 \% = \% \text{ loss on drying}$$

The results are depicted in table 1.

Table 1.

Batch No.	Initial weight (g)	Net weight (g)	Loss on drying (g)	Moisture content (%)
250701	5.005	4.792	0.213	4.26

B. Determination of water content

The water content of the pyrimetazol which had been dried as outlined above was determined by titration employing the Karl Fischer method. The water content of said pyrimetazol was 4.8 % indicating 1.14 mol of water per 1 mol of pyrimetazol ($x = 1.14$).

C. Recording of Infrared spectra

A Fourier Transform infrared spectra was recorded over the wave number range of 4000 to 400 cm^{-1} with Perkin Elmer spectrometer 1720X at a resolution of 4 cm^{-1} . A broad absorbance between 3600 – 3100 cm^{-1} and at about 1620 cm^{-1} indicates that water is bonded in the crystal lattice.

D. Recording of XRD-powder-spectrum

An XRD-powder spectrum was recorded. The spectrum and the recording parameters can be seen from the attached figure 1.

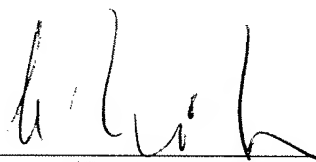
7. Results:

The absorbances between 3600 – 3100 cm^{-1} and at about 1620 cm^{-1} in the infrared spectra and the determined water content of pyrimetazol after drying as described above both indicate that water molecules are indeed bonded to pyrimetazol molecules via hydrogen bonds. Pyrimetazol as prepared according to the process described in US Patent Application Serial No. 10/772,033 is therefore obtained in form of hydrates.

Moreover, the signals in the XRD-powder spectrum show that the pyrimetazol as prepared according to the process described in US Patent Application Serial No. 10/772,033 is obtained in form of crystalline material.

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true, and further, these statements were made with the knowledge that wilful false statements and the like, so made, are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the Patent Application Serial No. 10/772,033 or any patent issued thereon.

Aachen, 12. Oktober 2006
(Date)


(Dr. Löbermann, Hartmut)